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<b>(54) Title:</b> SUSTAINED-RELEASE FORMULATIONS  <b>(57) Abstract</b>  Sustained-release formulations of a water soluble or highly water soluble drug comprising sufficient granules to provide a predetermined dose or number of doses. Each of the granules comprises said water soluble or highly water soluble drug and has a coating of a pharmaceutical wax or wax-like material over substantially its whole surface. The granules are optionally further provided with a coating of a polymer or other non-wax material deposited from an aqueous suspension or solution. A method for preparing the formulations is also provided.		

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SUSTAINED-RELEASE FORMULATIONS

This invention relates to sustained-release formulations of water soluble drugs, especially highly water soluble drugs. A method for preparing the formulations is also provided.

5           Some medical conditions are best treated by administration of a pharmaceutical which is formulated to allow the active substance or ingredient to act as quickly as possible. Such a formulation may comprise an injectable solution or a readily dissolvable tablet  
10 or capsule. This type of formulation is useful, for instance, for treating acute pain, such as headaches, or pain associated with sudden trauma, such as an accident.

          Other medical conditions are best treated by  
15 administration of a pharmaceutical in such a way as to sustain its action over an extended period of time. This type of administration is useful, for example, for treating chronic pain, such as that associated with rheumatic or arthritic conditions, or for the  
20 treatment of a chronic cardiovascular condition. It can be achieved by repeated administration of an immediate-release tablet or capsule at frequent intervals, for instance every four hours. However, this is generally inconvenient, especially during the  
25 night, when it is often necessary to awaken a patient to administer the tablet or capsule. In addition, such multiple dosing may lead to undesirable fluctuations in the plasma concentration of the active substance.

30           It has previously been proposed to produce a formulation which will release the active substance therein at a controlled rate such that the amount available in the body to treat the condition is

maintained at a relatively constant level over an extended period of time. Particularly suitable periods are twelve hours and twenty-four hours, since such formulations need only be taken once or twice a day to maintain an effective treatment of the condition. Such formulations are generally known as

5 "sustained-release formulations."

Many sustained-release formulations are already known, but there is no generally applicable method by which such formulations can be designed. Each formulation is dependent on the particular active

10 substance incorporated therein. In designing a formulation, it is generally necessary to take into account many factors, including the rates of absorption and clearance of the active substance, the interaction of the active substance with the

15 excipients and/or coatings to be used in the formulation, the solubility of the active substance and of the excipients and/or coatings, and the effects on the bioavailability of the active substance which may be caused by the excipients and/or coatings.

20 It is, however, not possible readily to predict whether any particular formulation will provide the desired sustained-release, and it is generally found necessary to carry out considerable experimentation to produce a sustained-release formulation having the

25 desired properties.

Additional difficulties arise when the pharmacologically active substance to be administered is soluble or highly soluble in water and other aqueous solutions. The term "soluble" as used herein

30 is to be understood as referring to substances which are soluble in up to 100 parts of water. Examples of highly water soluble drugs include isosorbide-5-mononitrate, chlorpheniramine maleate, dextropropoxyphene HCl, dihydrocodeine

35 tartrate, oxprenolol HCl, pheniramine maleate,

promethazine HCl, salbutamol sulphate and morphine sulphate.

Isosorbide-5-mononitrate, for example, is a vasodilator and is useful for the treatment of angina pectoris. Immediate-release and sustained-release formulations of this drug have previously been developed. Sustained-release formulations currently available in the United Kingdom include those sold under the names Imdur and Elantan LA.

Problems experienced in the development of sustained-release formulations of drugs such as isosorbide-5-mononitrate stem largely from their aforementioned high solubility. Attempts to coat beads or pellets (hereinafter referred to as "granules") of the drug with the usual polymers in aqueous solvents have resulted in products in which there is rapid migration of the drug from within the porous granules to the surface of the coating. It appears that some recrystallisation occurs while the coat is drying and this produces fine needles that penetrate the coating, thereby destroying its integrity and causing rapid release of the drug. The present inventors have surprisingly found that such effects can be avoided by first applying to the granules a coating (i.e. a sub-coat) of a drug migration controlling agent (DMCA).

According to the present invention there is provided a sustained-release formulation of a water soluble or highly water soluble drug comprising sufficient granules to provide a predetermined dose or number of doses, each of said granules comprising said water soluble or highly water soluble drug and having a coating of a pharmaceutical wax or wax-like material over substantially its whole surface. The pharmaceutical wax or wax-like material (hereinafter referred to simply as wax) acts as a DMCA, and is

typically a long chain alcohol, acid or ester, a paraffin wax, such as a hard paraffin wax or cetyl ester wax, or a silicone wax. The pharmaceutical wax preferably comprises a long chain alcohol, most preferably cetostearyl alcohol. Such materials are pharmaceutically acceptable for oral administration.

In a preferred embodiment of the invention, at least a proportion of the aforesaid granules are further provided with a coating of a polymer or other non-wax material deposited from an aqueous suspension or solution and covering substantially the whole surface thereof.

The invention further provides a method for preparing these sustained-release formulations and which comprises:-

- i) forming granules comprising the water soluble or highly water soluble drug;
- ii) providing each of the said granules with a coating of a pharmaceutical wax or wax-like material; and optionally
- iii) forming an aqueous suspension or solution comprising a polymer or other non-wax material; and
- iv) coating at least a proportion of the granules with the said suspension or solution. Most preferably, the coating of step iv) is applied in several stages, each layer of the coating being allowed to dry before the next layer is applied.

In the following description, all parts and percentages are by weight unless otherwise indicated.

This invention is based on the twin discoveries that:

5. 1) There is a tendency for a very soluble drug to migrate rapidly to the surface of a coating composed of the usual polymers, and
- 10 2) This can be overcome by the application of an initial coating of a pharmaceutical wax. The wax coating inhibits drug migration, but does not prevent water penetrating into the granules to dissolve the
- 15 patient.

A range of "waxes" were evaluated for their value in controlling the release of water soluble or highly water soluble drugs. The actual drug used in  
20 these tests was isosorbide-5-mononitrate. The results obtained are shown in Table I below. Witepsol H15 was clearly seen to be the least suitable for this drug, because even with 10% loading all of the drug was released after only 3 hours. Hard paraffin gave  
25 better results, but the long chain alcohols (and cetostearyl alcohol in particular) were found to be the most effective of the materials tested with isosorbide-5-mononitrate because they give most control over the release of this particular drug.

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Table 1: Effect of coatings and coating loading on release of isosorbide - 5 - mononitrate.

	Wax applied	Wax loading (%)	Eudragit loading (%)	Time for 100% release
5	Witepsol	1	0	15 min.
	"	2	0	15 min.
	"	3	0	15 min.
	"	4	0	30 min.
	"	5	0	30 min.
10	"	5	5	1.5 hr.
	"	5	10	2.0 hr.
	"	10	15	3.0 hr.
	"	10	20	3.0 hr.
	"	5	15	3.5 hr.
15	Hard Paraffin	5	15	1.0 hr.
	"	10	0	2.5 hr.
	"	10	10	11.0 hr.
	"	10	15	>12.0 hr.
	"	10	20	15 min.
20	Cetyl Alcohol	5	0	1.0 hr.
	"	5	10	15 min.
	"	10	0	1.0 hr.
	"	10	10	5.0 hr.
	"	10	15	7.0 hr.
25	"	10	20	30 min.
	Cetostearyl Alcohol	15	0	12.0 hr.
	"	15	15	>12.0 hr.
	"	15	20	

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Witepsol grade = Witepsol H15

Eudragit = Eudragit NE 30D

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It will be appreciated that the precise diameter and composition of the granules comprising the water soluble or highly water soluble drug will depend on the actual drug concerned and the time over which the formulation is designed to work. Generally, however, each of the granules will have a diameter of between 0.5 and 2.5 mm, preferably between 0.7 and 1.2 mm. Each of the granules has a coating of a pharmaceutical wax covering substantially the whole of its surface.

Turning now to the embodiment wherein at least a proportion of the granules are provided with a further coating of a polymer or other non-wax material, to some extent the diameter of the coated granules and the composition and amount of this further coating will each depend on the time over which the formulation is designed to work. Typically, however, each of the coated granules will have a diameter of between 0.5 and 2.5 mm, preferably between 0.7 and 1.2 mm. A suitable polymer coating, for example, comprises a water insoluble but water swellable acrylic polymer and a water soluble hydroxylated cellulose derivative. Typically, for every 100 parts of the water insoluble but water swellable acrylic polymer present in the coating, there will be from 20 to 70 parts of the water soluble hydroxylated cellulose derivative. The weight of this polymer coating will usually be from 2 to 25% of the weight of the underlying granule. Preferably, the weight of this coating is from 2 to 10% of the weight of the granule.

The formulations of this invention are characterised by the presence of granules which bear a coating of a pharmaceutical wax. It is to be understood that some or all of the granules may also have a further coating of a polymer or other non-wax

material. As will be readily appreciated, by varying the proportion of granules with a further coating it is possible to produce a range of formulations with different release profiles. It is within the ability of persons skilled in the art, through routine trial and experimentation, to determine the proportions of such coated: non-coated granules needed to achieve particular release characteristics.

In addition to the pharmacologically active substance, i.e. a water soluble or highly water soluble drug, the formulations also preferably contain a bulking agent such as microcrystalline cellulose. This is a well known form of cellulose which is partially depolymerised. A particularly suitable microcrystalline cellulose is sold under the name Avicel (a registered trade mark). However, other conventional bulking agents may also be used, as will be readily apparent to those skilled in the art.

The formulations may also contain a diluent, such as lactose. A capillary-active agent, such as sodium carboxymethylcellulose, which is sold under the name Ac-Di-Sol (a registered trade mark), may additionally be included. These components are used in conventional amounts. If desired, the formulations of this invention may also contain colouring agents, sweetening agents and flavouring agents.

A polymer coating, when present, preferably comprises about 30 parts of a hydroxylated cellulose derivative. If too much is present, the coating may become too sticky and the rate of release may become too high. If too little is present, the rate of release may be too low. A particularly suitable hydroxylated cellulose derivative is hydroxypropylmethyl cellulose having a degree of substitution of 28 to 30% of methoxy groups and 7 to 12% of hydroxy groups. However, other equivalent

materials such as hydroxypropyl, hydroxyethyl or hydroxymethyl celluloses can be used.

The acrylic polymer component of the polymer coating is preferably neutral and may comprise a  
5 homopolymer or a copolymer, for instance of acrylic acid esters or methacrylic acid esters. Preferably, the acrylic polymer is provided as an aqueous dispersion. A particularly suitable acrylic polymer  
10 is sold under the name Eudragit (a registered trade mark), which comprises a copolymer of acrylic and methacrylic acid esters and which is usually supplied as an aqueous dispersion containing approximately 30% solids.

The formulations of this invention can  
15 typically be prepared in the following manner. The pharmacologically active substance, i.e. a water soluble or highly water soluble drug, is blended with other constituents, such as a bulking agent and a diluent. The blending is conveniently performed by  
20 mixing the components in a dry blender. Some water is next added to produce a slightly cohesive product. This is then extruded, chopped into suitable lengths, spheronised and dried to produce the desired granules. These are then coated, suitably in a coating pan, with  
25 a molten pharmaceutical wax and left to cool so that individually coated granules are produced.

If desired, a further coating of a polymer or other non-wax material is then applied to the granules. In the case of polymer coated granules a  
30 suitable coating is prepared, for example, by forming a solution of a hydroxylated cellulose derivative and mixing it with a dispersion of an acrylic polymer. The aqueous mixture is then used to coat the dried granules, prepared as described above, and these are  
35 subsequently dried to produce coated granules.

Preferably, the coated granules are then sieved to ensure that they are in the correct size range.

5 The resulting formulations of this invention may be supplied loose with a means for dispensing a measured amount, for instance to be sprinkled on food. Alternatively, they may be provided in sachets containing measured amounts. More preferably, however, the formulations are placed in measured amounts in readily soluble capsules. The capsule may be any of  
10 those already known in the art, and may, for instance, comprise a thin gelatin skin. Preferably, the capsule contains a sufficient amount to provide a conventional dose of the pharmacologically active substance. The granules may, if desired, be formed into tablets  
15 using conventional tableting machinery.

It has thus surprisingly been found that the presence of a coating of a pharmaceutical wax, most preferably cetostearyl alcohol, assists in the formulation for sustained-release administration of  
20 water soluble or highly water soluble drugs. Examples of such drugs include those mentioned above.

The present invention will now be illustrated by the following Examples and which refer to formulations of representative highly water soluble  
25 drugs. The Examples are by way of illustration only; they do not necessarily represent fully optimised formulations. The formulations described below were developed using the OSAT system developed by the inventors at the University of Bradford.  
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EXAMPLE 1

5 A review of the literature on isosorbide-5-mononitrate suggests that the 24-hour blood level profile should ideally consist of a period following the administration of a dose where the plasma level rises rapidly to an effective range, is maintained there for about 16 hours and is followed by an essentially drug free period (i.e. a low or zero drug concentration) before the next dose. Since the half-life is about 4 hours, release from the dose form should be completed well before the end of the 16-hour peak phase. Assuming that a suitable active pharmacological blood level is around 400 ng/ml and the inactive phase begins at about 100 ng/ml, this corresponds to a period after complete release from the formulation of about two half-lives, i.e. 8-9 hours. The following account describes the development of a multi-particulate coated bead formulation in capsules, mixed with fast-release beads, which meets these requirements when assessed in vitro by dissolution measurements.

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OSAT FORMULATIONS 1 and 21) PELLET MANUFACTURE

* Isosorbide - 5 - mononitrate mixture	42%	* 800g
Microcrystalline cellulose	58%	1120g
Water (to bind)		<u>1000ml</u>
	<u>100%</u>	<u>1920g</u>

\* Isosorbide - 5 - mononitrate diluted 60:40 with lactose (lot 258 P054).

Microcrystalline cellulose - Avicel PH101 (lot 710161).

\* Equivalent to 480g isosorbide - 5 - mononitrate.

The dry ingredients were mixed together using a Hobart mixer. Water was added in portions until the components began to bind and the mixture was of a suitable consistency for extrusion. The mixture was extruded using an Alexanderwerk extruder to produce 1mm slugs which were then spheronised for 1 minute in a Caleva spheroniser. The resulting pellets were dried overnight at room temperature. The pellets were sieved and those with diameters between 0.7 and 2.0mm were collected.

2) PELLET COATING

Pellets were rotated in a Manesty 16 inch copper coating pan together with 15% w/w cetostearyl alcohol B.P. (Evans, lot 8BY9547). A hot air gun was employed to raise the temperature in the pan to  $-55^{\circ}\text{C}$  to allow the cetostearyl alcohol to melt. The pellets became coated with the liquid wax as they rotated. The heat source was then removed and, as the wax cooled it formed a smooth coat around individual pellets. The pellets were left to cool whilst being rotated in the pan.

A portion of the cetostearyl alcohol coated pellets was given an additional coat of 20% w/w Eudragit NE 30D (calculated with respect to uncoated pellet dry weight). The pellets were rotated in the copper coating pan and the Eudragit NE 30D (Rohm Pharma, lot 12-88-1276) was applied as a 30% aqueous dispersion in four equal portions. After each portion had been added, and that stage of the coating procedure completed, the pellets were removed from the pan and placed in an oven at  $35^{\circ}\text{C}$  for approximately 3 hours to ensure that each layer of the coating had dried completely before the next one was added. When the final layer of the coat had been applied the pellets were left to dry overnight in the oven at  $35^{\circ}\text{C}$ .

3) FORMULATIONS - for dissolution studiesFormulation 1

Pellets (cetostearyl alcohol + Eudragit coated)	151mg	=	28mg	IS-5-MN
Pellets (cetostearyl alcohol coated)	55mg	=	12mg	IS-5-MN
	<u>206mg</u>	=	<u>40mg</u>	IS-5-MN

The dose of isosorbide - 5 - mononitrate was 40mg per capsule. 70% (28mg) of the dose was contained in pellets coated with 15% cetostearyl alcohol + 20% Eudragit and 30% (12mg) of the dose was contained in pellets coated with 15% cetostearyl alcohol only.

Formulation 2

Pellets (cetostearyl alcohol + Eudragit coated)	173mg	=	32mg	IS-5-MN
Pellets (cetostearyl alcohol coated)	37mg	=	8mg	IS-5-MN
	<u>210mg</u>	=	<u>40mg</u>	IS-5-MN

The dose of isosorbide - 5 - mononitrate was 40mg per capsule. 80% (32mg) of the dose was contained in pellets coated with 15% cetostearyl alcohol + 20% Eudragit and 20% (8mg) of the dose was contained in pellets coated with 15% cetostearyl alcohol only.

Commercial Formulations

Indur R

60mg sustained release tablet  
Astra Pharmaceuticals Limited  
PL0017/0226  
PA9/36/1  
Lot OC-66

Elantan R LA50

50mg sustained release capsule  
Schwarz Pharmaceuticals Limited  
PL4438/0015  
PA271/1/3  
Lot 70375

DISSOLUTION TESTING1) U.V. Calibration measurements**Apparatus:**

Hewlett Packard diode array spectrophotometer. Model HP451A  
1cm flow cell.

Drug/lactose mixture (IS-5-MN 40mg) was dissolved in water (IL). The absorption spectrum was measured between 190 and 820nm at 37°C with distilled water as the reference. One peak was observed at 196nm ( $d = 0.890$ ).

Interference by lactose in the solution was found to be negligible. The other insoluble components were assumed to be non-interfering.

Using this reference datum in the dissolution studies at 12 hours (complete dissolution), Imdur 60mg was found to contain 60.7mg of IS-5-MN and Elantan LA50 47.0mg, uncorrected for capsule weight content in both cases. Excipients in these formulations were thus considered unlikely to interfere with dissolution studies.

2) Test Conditions

Dissolution tests were carried out on formulations 1 and 2 using an automated U.S.P. dissolution system. Imdur and Elantan LA50 were tested by the same method.

**Apparatus:**

Caleva Dissolution apparatus model 6ST

Watson Marlow pump

Hewlett Packard diode array spectrophotometer model HP451A with 7 cell transport acquisition

1cm flow cells

Hewlett Packard twin disc drive model HP9121.

**Conditions**

dissolution medium	:	distilled water
volume	:	1000ml
pH	:	5.7
temperature	:	37°C
vessels	:	round bottom
stirrers	:	baskets
revolution speed	:	100rpm
detection wavelength	:	196nm
duration of test	:	12 hours
concentration of standard solution	:	40mg/I. isosorbide - 5 - mononitrate.

3) Results

Dissolution profiles are shown in Figures 1 to 5 normalised to 100% release at 12 hours.

Figure 1

Formulation 1

Figure 2

Formulation 2

Figure 3

Pellets coated with cetostearyl alcohol

Pellets coated with cetostearyl alcohol and Eudragit NE30D

Figure 4

Indur

Elantan LA50

Figure 5

Formulation 1

Formulation 2

Indur

Elantan LA50

Figure 3 shows the dissolution profiles of the two types of coated pellets which were mixed to produce Formulations 1 and 2. By changing the proportion of each type of pellet in the mixture, the dissolution characteristics of the dose were changed to produce formulations which gave the required dissolution profiles (Figures 1 and 2).

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The dissolution profile of the sustained release capsule Elantan LA50 (Figure 4) was considered to be a suitable model with which to compare the profiles of Formulations 1 and 2 as this product has been shown to achieve accepted therapeutic levels of isosorbide - 5 - mononitrate in the blood. Figure 5 showed a comparison of the dissolution profiles of Formulations 1 and 2 with the commercial products Elantan LA50 and Imdur. Formulation 1 gave a profile closest to that of Elantan LA50.

IN VITRO - IN VIVO SIMULATIONS1) Methods and data sources

The dissolution data in Section 3.3 were used to predict in vivo blood level-time profiles using the pharmacokinetic data recorded by Major et al (Clin.Pharmacol Ther. 1984, 35, 643-659) and graphical and computer methods. Predictions from the in vitro measurements were then compared with in vivo profiles published for Elantan LA50 in The American Journal of Cardiology, 1988 and in the Schwarz product literature booklet, and for Imdur from the Astra booklet. Predictions for OSAT formulations 1 and 2 (pellet combinations 70:30 and 80:20) formulations were also made but these await comparison with volunteer studies.

2) RESULTS AND DISCUSSION:A. Elantan LA

Figure 6 shows two experimental in vivo profiles from the American Journal of Cardiology and the Schwarz booklet (although these are multidose studies cumulation is likely to be negligible). They are in good agreement. The computer predicted curve was obtained by assuming an initial infusion over  $\frac{1}{2}$  hr of 19.6mg of drug followed by 30.4mg infused over 7.6hr at 4mg/hr (from the dissolution results). The other predicted curve was derived by a graphical technique with an initial input as for the computer method, followed by amounts each hour calculated from the dissolution data. Drug remaining for release after 8 hours (5 per cent) was assumed to be absorbed by 12 hours. Both predicted curves were fairly close to the experimental data, the computer method being the better. It is possible that the kinetic parameters for the subjects in Major's study were somewhat different from the subjects in the other two experimental reports thus partly accounting for the differences. For development purposes the agreement is reasonably satisfactory.

B.     Imdur

The in vitro - in vivo comparison is shown in Figure 7. Computer data were generated from an input over the first half hour of 19.3mg followed by infusion of 40.7mg at 6mg/hr for 6.8 hours. This release pattern was estimated from the dissolution data although it was actually slower in the 5-7 hour period. Agreement with the in vivo data is reasonable over the first 12 hours but there is a large discrepancy at 24 hours. The Astra data only shows a single point after 12 hours and this may be inaccurate for some unknown reason.

C.) OSAT Formulations 1 and 2

Predictions were obtained as before by the graphical and computer methods. For the computer prediction 15.2mg was assumed infused over the first half hour followed by 25 mg at 3.0 mg/hr over 8.33 hours for formulation 1 (70:30 pellet ratio) and 10.8 mg followed by 29.2 mg over 9.7 hours (also 3.0 mg/hr) for formulation 2. Results are shown in Figure 8.

The prediction probably indicates a drug free period of about 6 hours. If a longer period is required a pellet ratio of 60:40 could be considered, or possibly a slightly faster release for the Eudragit-coated fraction.

EXAMPLES 2 and 31) PELLET MANUFACTURE

All pellets were manufactured on a bench scale according to the following formula.

Drug	:	2.0g
Avicel PH101	:	2.0g
Distilled water	:	as required.

The dry ingredients were mixed together and distilled water added slowly until a thick paste formed. The paste was then pressed into plastic moulds and allowed to air dry for approximately 12hrs before ejecting the formed pellets.

## 2) PELLET COATING

### Wax coating

A known quantity of pellets (approx 2g) was rotated in a small copper coating pan together with 20% w/w wax\*. A hot air gun was employed to raise the temperature of the pan to allow the wax to melt. The pellets became coated with liquid wax as they rotated. The heat source was then removed and as the wax cooled it formed a smooth coat around individual particles.

[\*approx 15% w/w wax coating achieved.]

### Eudragit coating

A known quantity of pellets (approx 2g) were rotated in a small copper coating pan. An aqueous dispersion of Eudragit (NE30D) was added dropwise in small portions, drying was assisted by a gentle stream of cool air directed into the pan. At regular intervals the pellets were removed and weighed until the desired level of coating was reached.

## 3) DISSOLUTION TESTING

### Assay method

To follow drug release from the pellets, the dissolution medium was assayed by measuring the change in its absorbance at a specific wavelength. Several absorption peaks were identified for each drug, and the peaks at 274nm (for oxprenolol hydrochloride) and 284nm (for dihydrocodiene tartrate) were chosen as suitable for the purpose because they both exhibit a linear increase in absorbance with increasing drug concentration. Interference from Avicel PH101, the excipient used in pellet manufacture, was shown to be negligible.

4) TEST CONDITIONS

Dissolution tests were performed using an automated U.S.P. dissolution system.

The mass of pellets used for each test was such that at 100% release, drug concentration in the dissolution fluid was approximately 25mg/l and 50mg/l for oxprenolol hydrochloride (Example 2) and dihydrocodeine tartrate (Example 3), respectively.

APPARATUS

Caleva dissolution apparatus model 6ST

Watson Marlow pump

Hewlett Packard diode array spectrophotometer model

HP8451A with 7 cell transport acquisition

CONDITIONS

Dissolution medium	:	distilled water
Volume	:	1000ml
Temperature	:	37°C
Vessels	:	flat bottomed
Stirrers	:	baskets
Revolution speed	:	100rpm
Duration of test	:	12hrs
Detection wavelength	:	Oxprenolol hydrochloride 274nm Dihydrocodeine tartrate 284nm

5) RESULTS

The dissolution profiles for drug-wax combinations are shown in the following order.

Oxprenolol hydrochloride :	Stearyl alcohol (Figure 9)
(Example 2) :	Tristearin (Figure 10)
:	Cetostearyl alcohol (Figure 11)

: Witepsol E85 (Figure 12)

: Dynasan 118 (Figure 13)

5 Dihydrocodeine tartrate : Stearyl alcohol (Figure 14)  
(Example 3) : Cetostearyl alcohol (Figure 15)  
: Witepsol E85 (Figure 16)  
: Dynasan 118 (Figure 17)

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SURFACE CHARACTERISTICS OF THE PELLETS

Examination method - microscopic

Magnification : 10x

Illumination : Natural

Pellets coated with Eudragit NE30D only

10 The Eudragit NE30D coat on some oxprenolol hydrochloride and dihydrocodeine tartrate pellets appeared irregular and poorly formed. No spikes of recrystallised drug were observed penetrating from the core though the Eudragit NE30D coat.

Pellets coated with wax and Eudragit NE30D

15 The Eudragit NE30D coat on some of the oxprenolol hydrochloride and dihydrocodeine tartrate pellets appeared to be of a higher quality in that it  
20 was smoother and more evenly formed.

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6) SUMMARY OF RESULTS

On coating pellets of drug with an aqueous dispersion of Eudragit they frequently softened and fragmented. The presence of a waxy coat prevented this and made coating with Eudragit easier.

Drying of the Eudragit-coated pellets was initially performed by passing a stream of warm air over the pellets as they rotated in the coating pan. However, as the pellets dried they became extremely adhesive and formed large agglomerates. It was found that if a stream of cool air was used it prevented this and also provided an acceptable drying rate.

From the dissolution studies, it can be seen that coatings of wax and Eudragit significantly affect the rate of release of the drug. All pellets remained intact during dissolution testing, except those with no wax/Eudragit coating. On crushing the pellets after a 12 hour dissolution test, more drug was released, confirming that the wax/Eudragit coatings used are effective in slowing and maintaining release of the drug over longer periods than 12 hours, although in some cases there is evidence of convergence to an asymptote at less than 100% release.

The dissolution profiles revealed that the presence of a waxy coat alone does not significantly retard drug release; thus any retardation in drug release must be due to the Eudragit coating. In pellets without a waxy coat, the Eudragit had little effect on the dissolution profiles, whereas on wax coated pellets with the same degree of Eudragit coating the rate of drug release was reduced.

Microscopic examination of Eudragit coats on waxed and unwaxed pellets showed that on some of the unwaxed pellets the quality of the coating was poor.

No recrystallised drug was seen to protrude through the coat; however it is possible that drug recrystallisation has occurred within the coat disrupting its structure; hence its poor appearance (in some cases) and rapid release characteristics.

5 It is clear that coating of pellets containing oxprenolol hydrochloride and dihydrochloride tartrate with Eudragit NE30D alone does not have the desired effect on the dissolution  
10 profile (retardation of release) probably due to poor formation of the coating structure during preparation.

The addition of a layer of waxy material before coating with Eudragit prevents this; in this way drug release can be satisfactorily retarded.

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CLAIMS

1. A sustained-release formulation of a water soluble or highly water soluble drug comprising sufficient granules to provide a predetermined dose or number of doses, each of said granules comprising said water soluble or highly water soluble drug and having a coating of a pharmaceutical wax or wax-like material over substantially its whole surface.

2. A formulation as claimed in claim 1, wherein the pharmaceutical wax is a long chain alcohol, acid or ester, a paraffin wax or a silicone wax.

3. A formulation as claimed in claim 1, wherein the pharmaceutical wax is a cetyl ester wax or hard paraffin wax.

4. A formulation as claimed in claim 1, wherein the pharmaceutical wax is cetostearyl alcohol.

5. A formulation as claimed in any one of claims 1 to 4, wherein all or some of the granules are further provided with a coating of a polymer or other non-wax material deposited from an aqueous suspension or solution and covering substantially the whole surface thereof.

6. A formulation as claimed in claim 5, wherein the coating is a polymer coating and comprises 100 parts of a water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative, the weight of this coating being from 2 to 25% of the weight of the underlying granule.

7. A formulation as claimed in claim 5 or claim 6, which provides sustained-release over a period of up to 48 hours.

8. A formulation as claimed in claim 5 or claim 6, wherein the diameter of the granules coated with the polymer or other non-wax material is between 0.5 and 2.5 mm.

9. A formulation as claimed in claim 6, wherein the diameter of the polymer coated granules is between 0.7 and 1.2 mm, the polymer coating contains from 20 to 40 parts of the water soluble hydroxylated cellulose derivative, and the weight of said coating is between 2 and 10% of the weight of the underlying granule.

10. A formulation as claimed in claim 6, wherein the polymer coating contains 30 parts of the hydroxylated cellulose derivative and which is hydroxypropylmethyl cellulose having a degree of substitution of 28 to 30% of methoxy groups and 7 to 12% of hydroxy groups.

11. A formulation as claimed in any one of the preceding claims, wherein the granules are contained within a capsule.

12. A formulation as claimed in any one of claims 1 to 10, wherein the granules are in tablet form.

13. A formulation as claimed in any of the preceding claims, wherein the drug is isosorbide-5-mononitrate, chlorpheniramine maleate, dextropropoxyphene HCl, dihydrocodeine tartrate, oxprenolol HCl, pheniramine maleate, promethazine HCl, salbutamol sulphate or morphine sulphate.

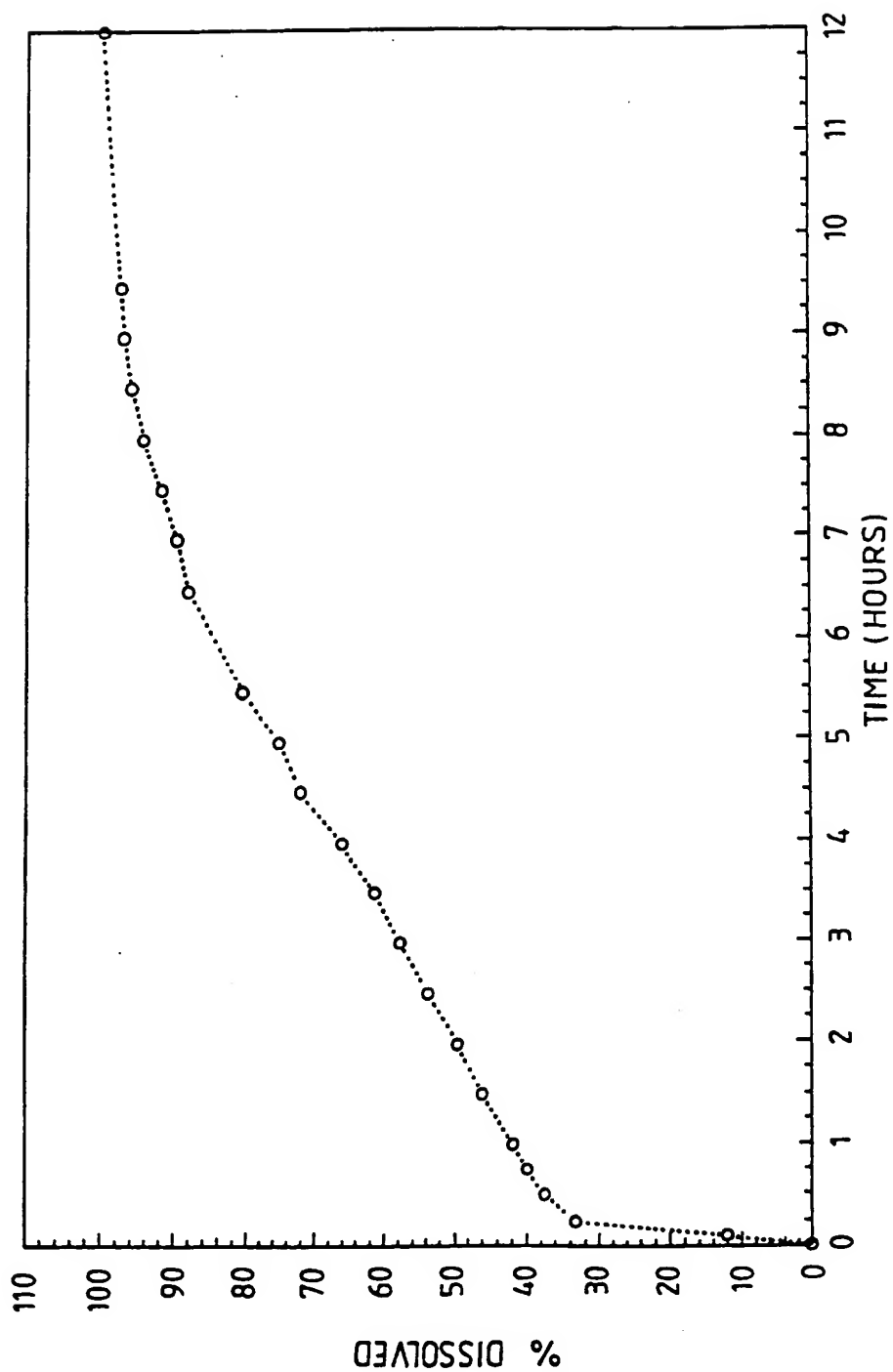
14. A formulation as claimed in any one of claims 1 to 12, wherein the drug is isosorbide-5-mononitrate.

15. A method for preparing a sustained-release formulation of a water soluble or highly water soluble drug and which comprises:-

- i) forming granules comprising said water soluble or highly water soluble drug;
- ii) providing each of the said granules with a coating of a pharmaceutical wax or wax-like material; and optionally
- iii) forming an aqueous suspension or solution comprising a polymer or other non-wax material, and
- iv) coating at least a proportion of the granules with the said suspension or solution.

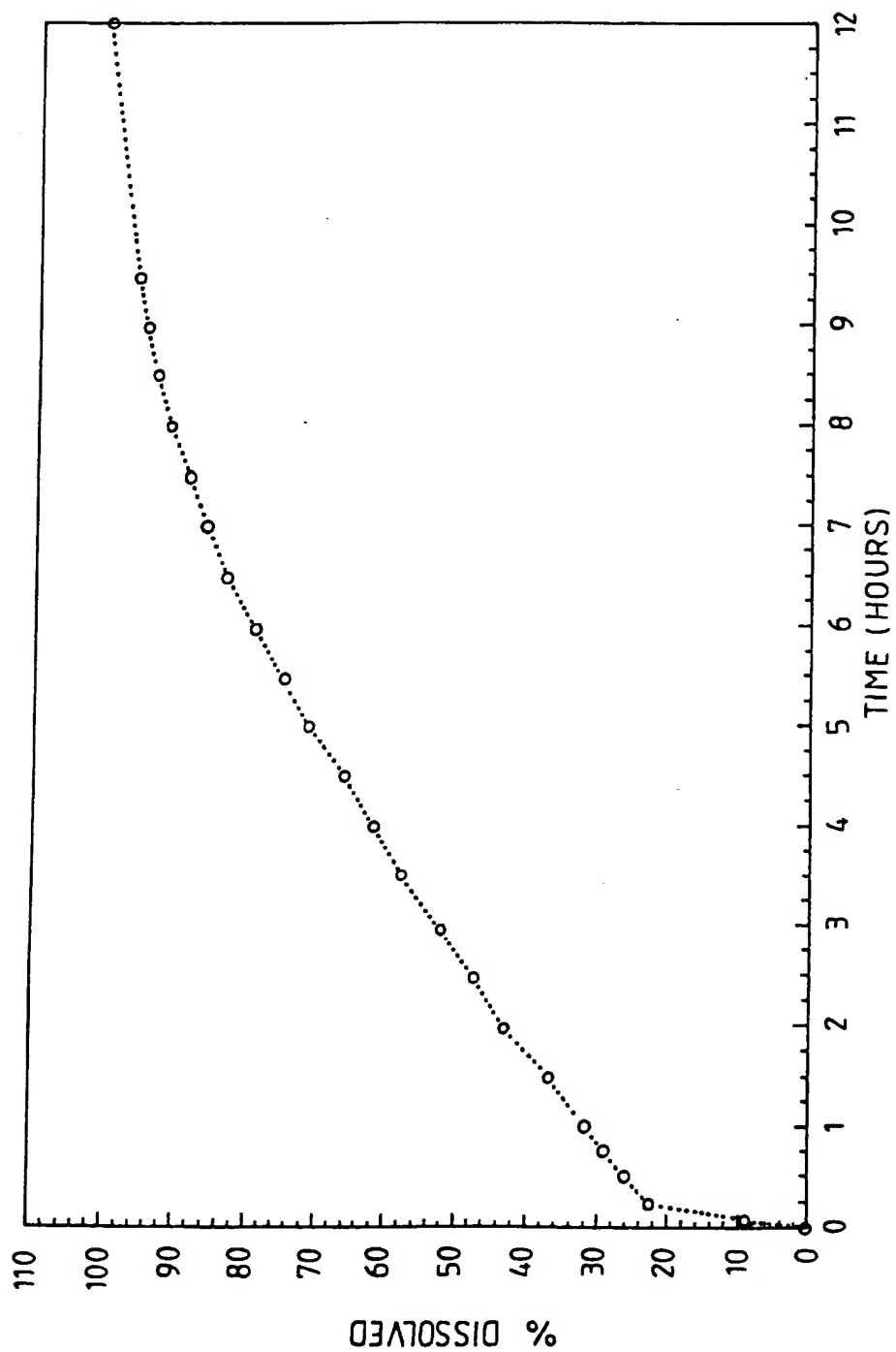
16. A method as claimed in claim 15, wherein the coating of step iv) is applied in several stages, each layer of the coating being allowed to dry before the next layer is applied.

1/17



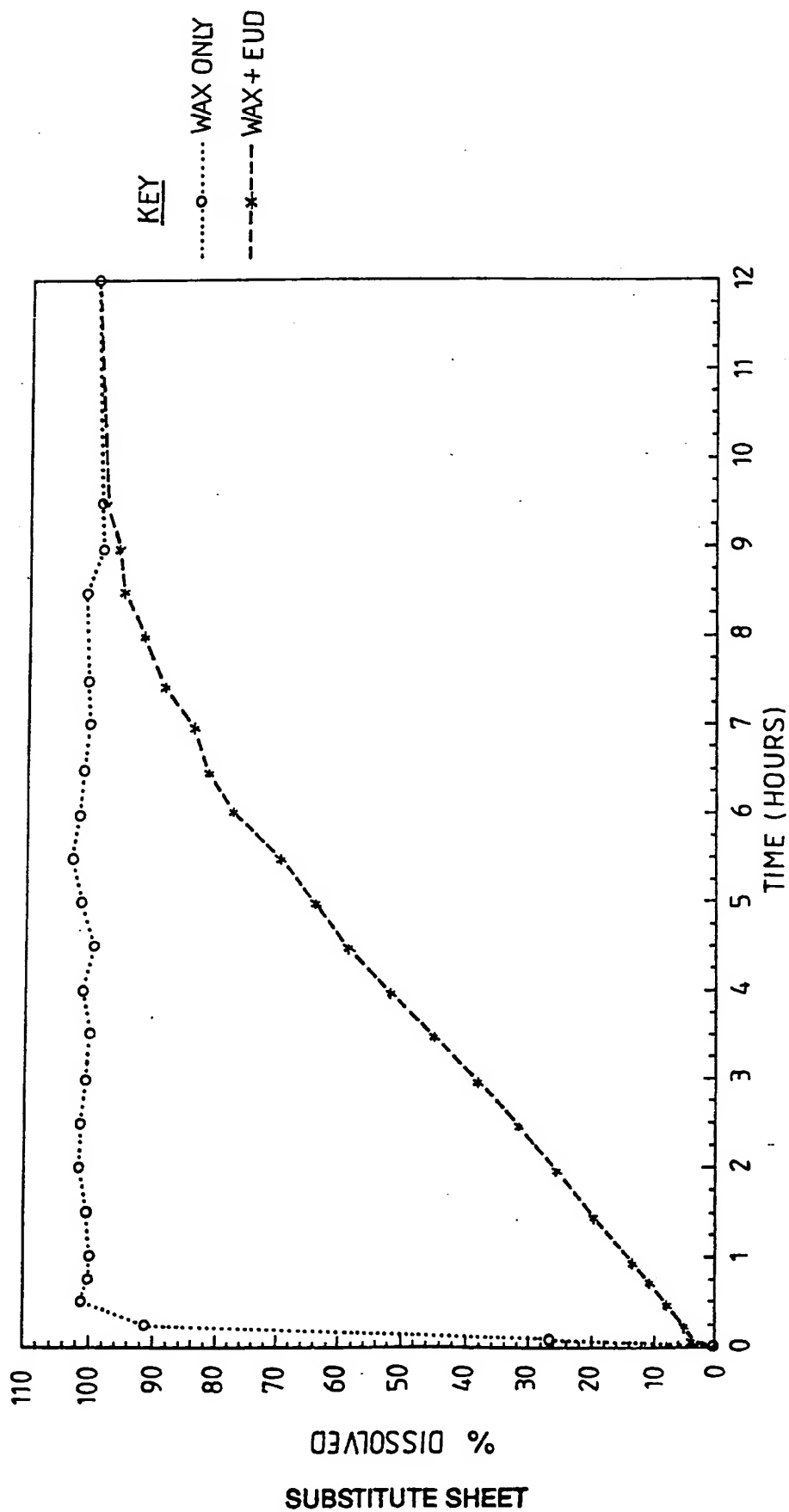
**Fig. 1** DISSOLUTION PROFILE FOR ISOSORBIDE-5-MONONITRATE  
FORMULATION 1 (70:30 MIX)

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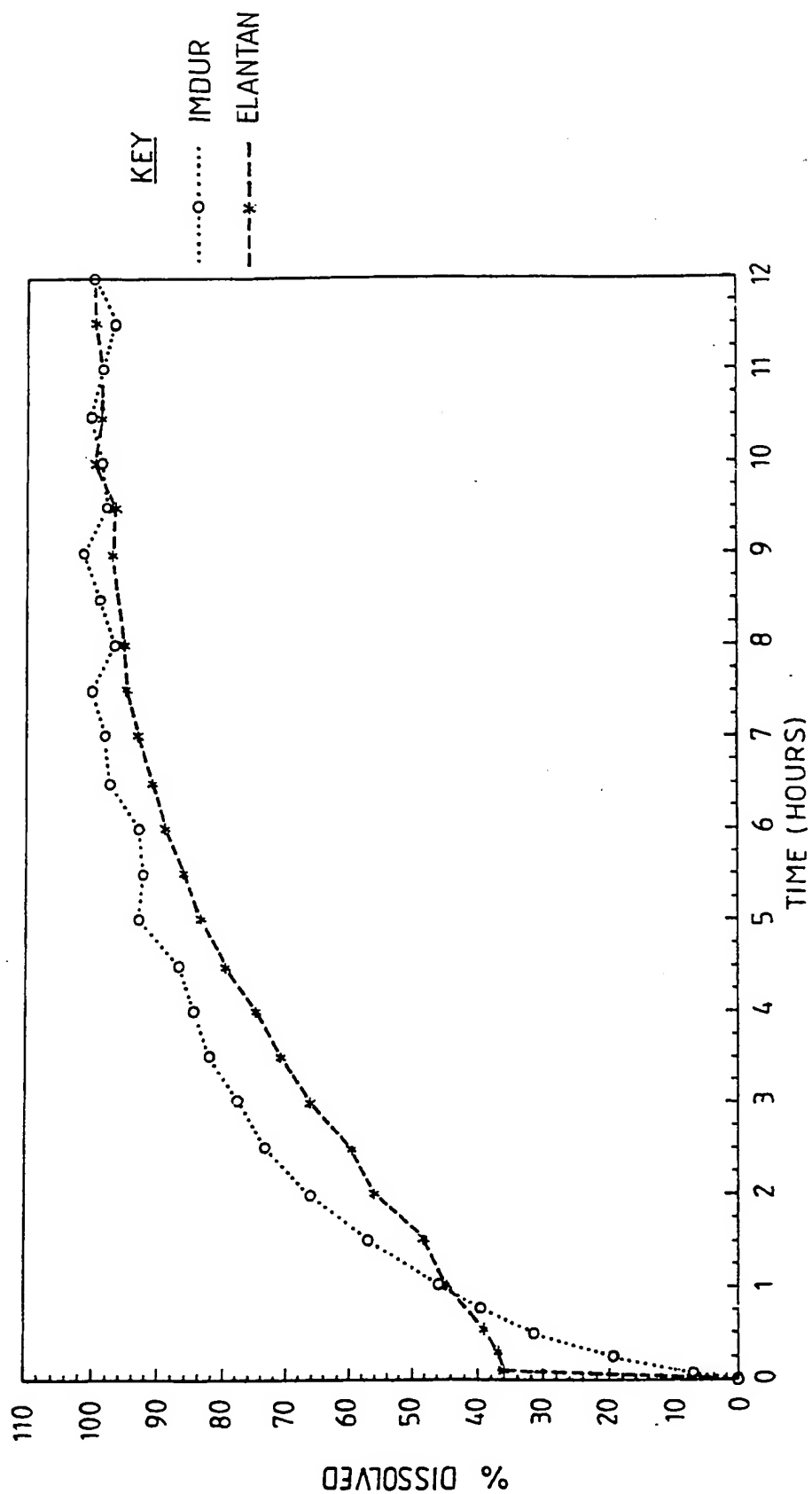
**Fig. 2** DISSOLUTION PROFILE FOR ISOSORBIDE-5-MONONITRATE  
FORMULATION 2 (80:20 MIX)

3/17



**Fig.3** DISSOLUTION PROFILES FOR  
ISOSORBIDE-5-MONONITRATE FORMULATIONS

4/17



**Fig.4** DISSOLUTION PROFILES FOR COMMERCIAL  
ISOSORBIDE-5-MONONITRATE PRODUCTS

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SUBSTITUTE SHEET

5/17

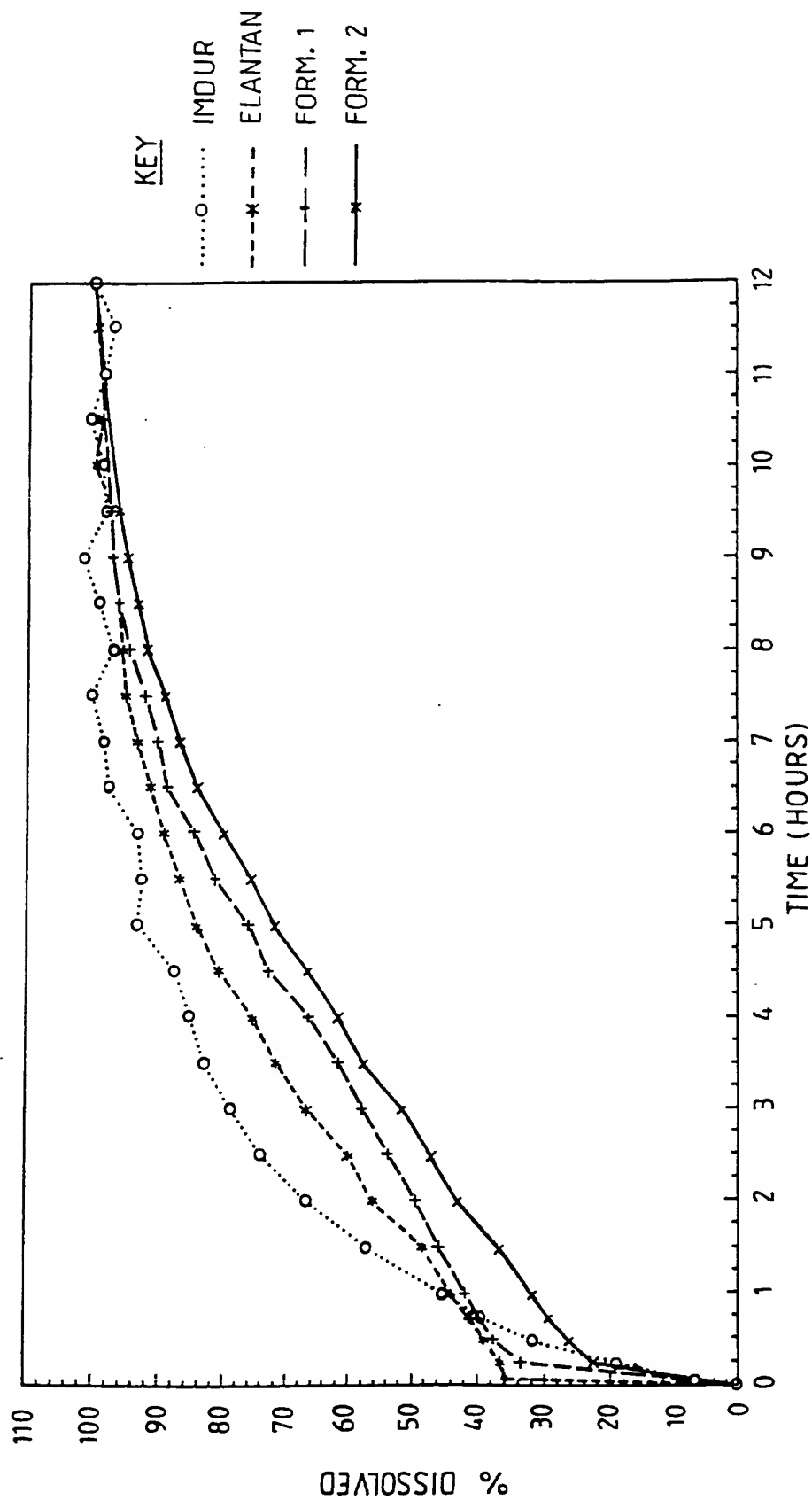
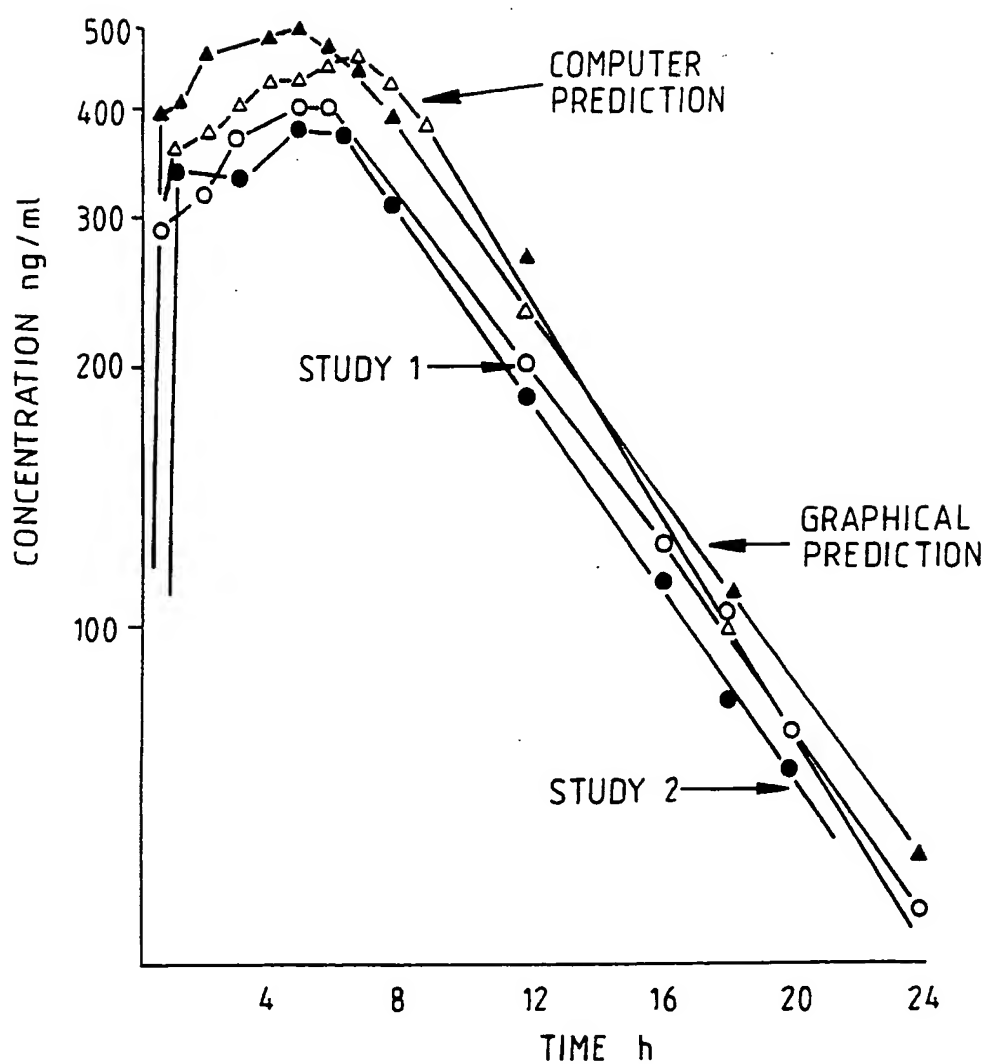


Fig. 5 DISSOLUTION PROFILES FOR ISOSORBIDE 5-MONONITRATE FORMULATIONS AND COMMERCIAL PRODUCTS

6/17

Fig.6

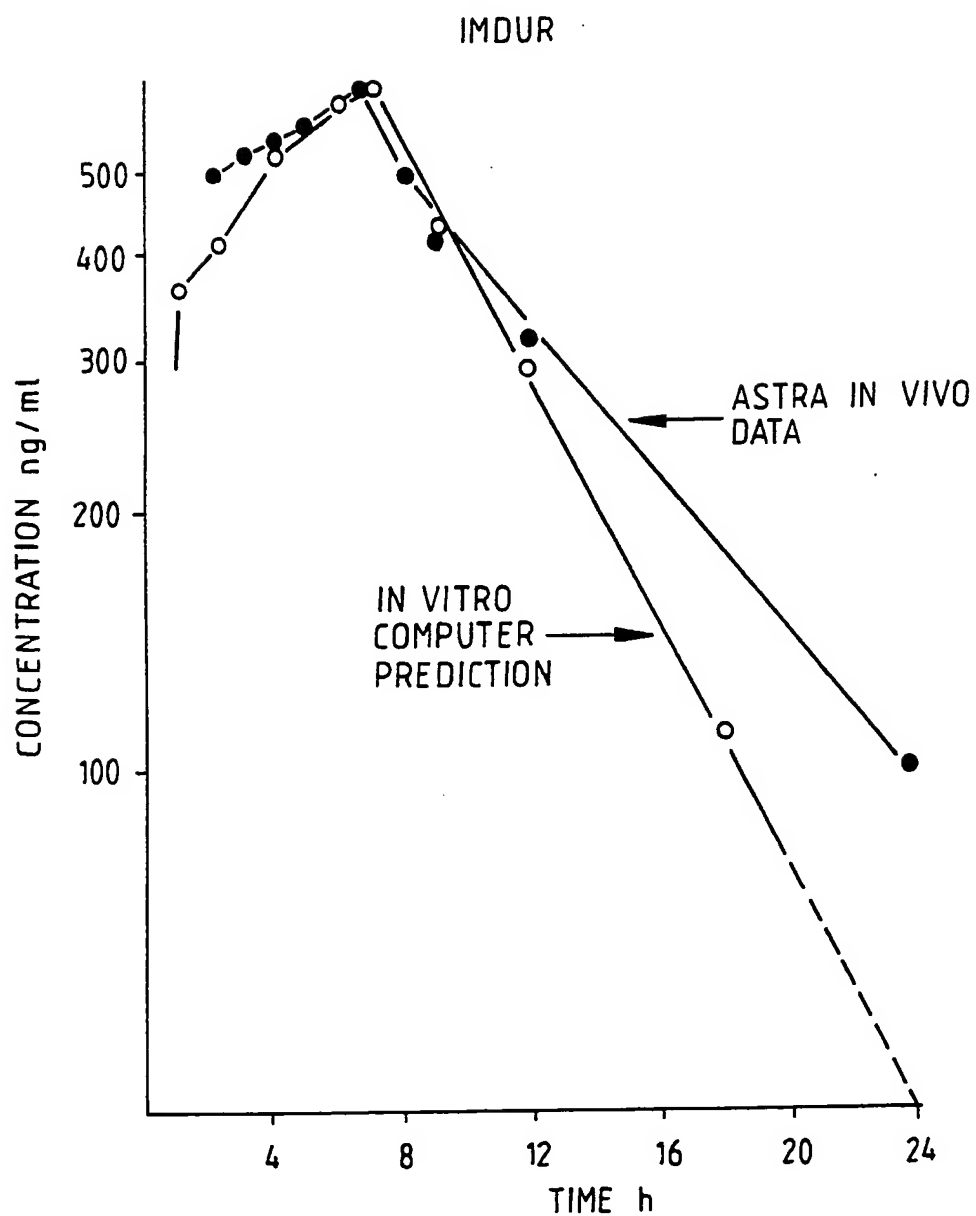
ELANTAN LA 50



in vitro predicted blood level-time curves for Elantan LA 50 compared with experimental in vivo data. Study 1 Amer.J. of Cardiology, 61, 12E, 1988. Study 2 Schwarz Product Literature on Elantan LA 50.

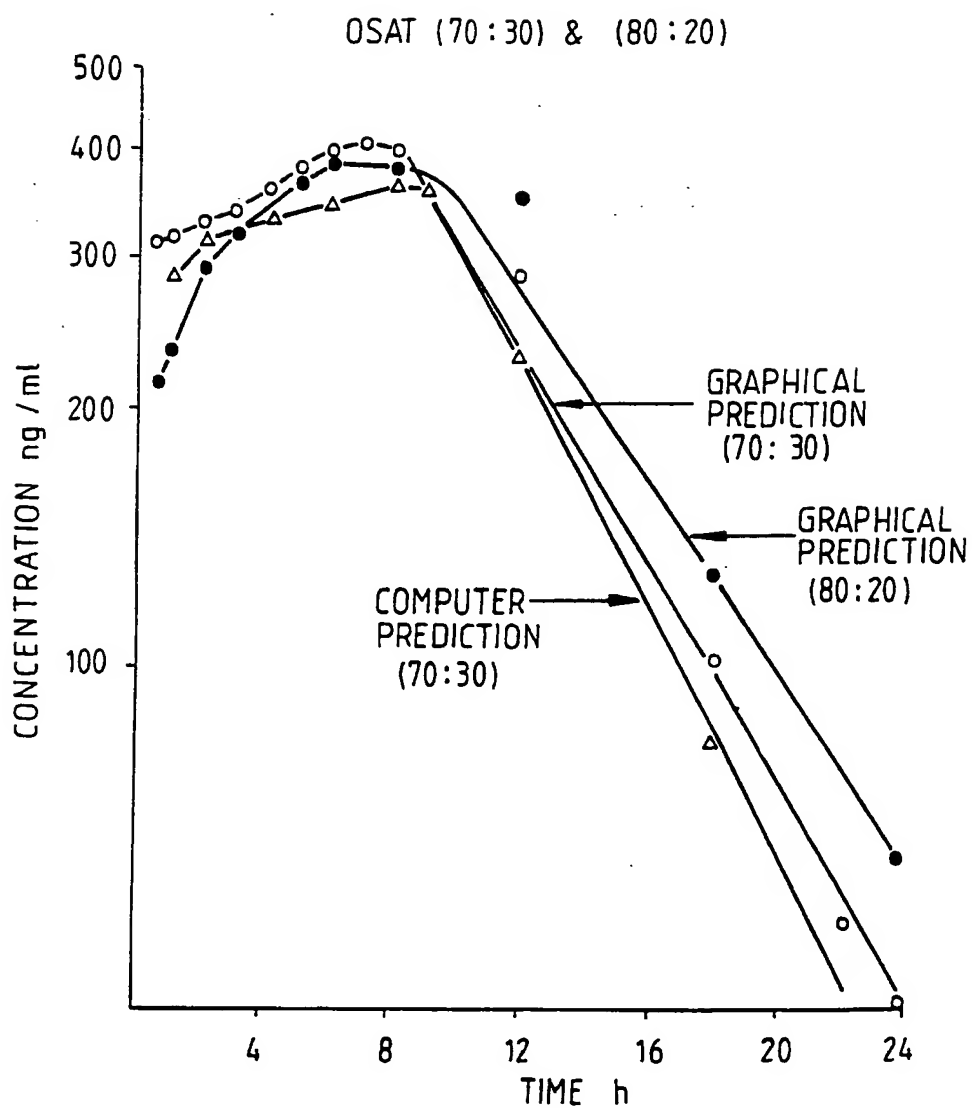
7/17

Fig.7



In vitro predicted blood level-time curves for Imdur compared with in vivo (Astra) experimental data.

8/17

*Fig.8*

In vitro predicted blood level-time curves for OSAT formulation 1 (70:30) and OSAT formulation 2 (80:20), graphical and computer methods.

9/17

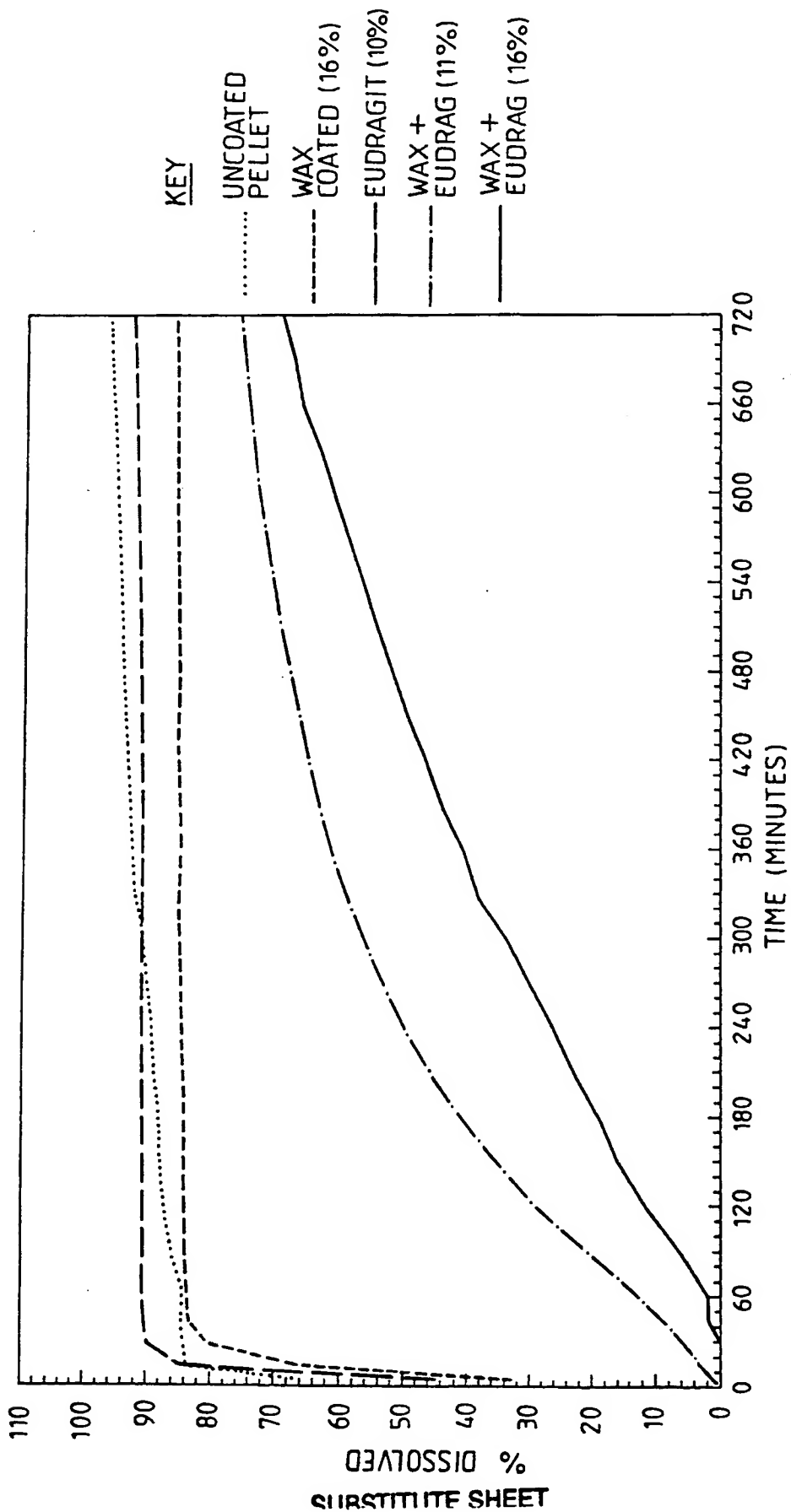


Fig. 9 OXPRENOLOL HYDROCHLORIDE DISSOLUTION RESULTS  
WAX: STEARYL ALCOHOL

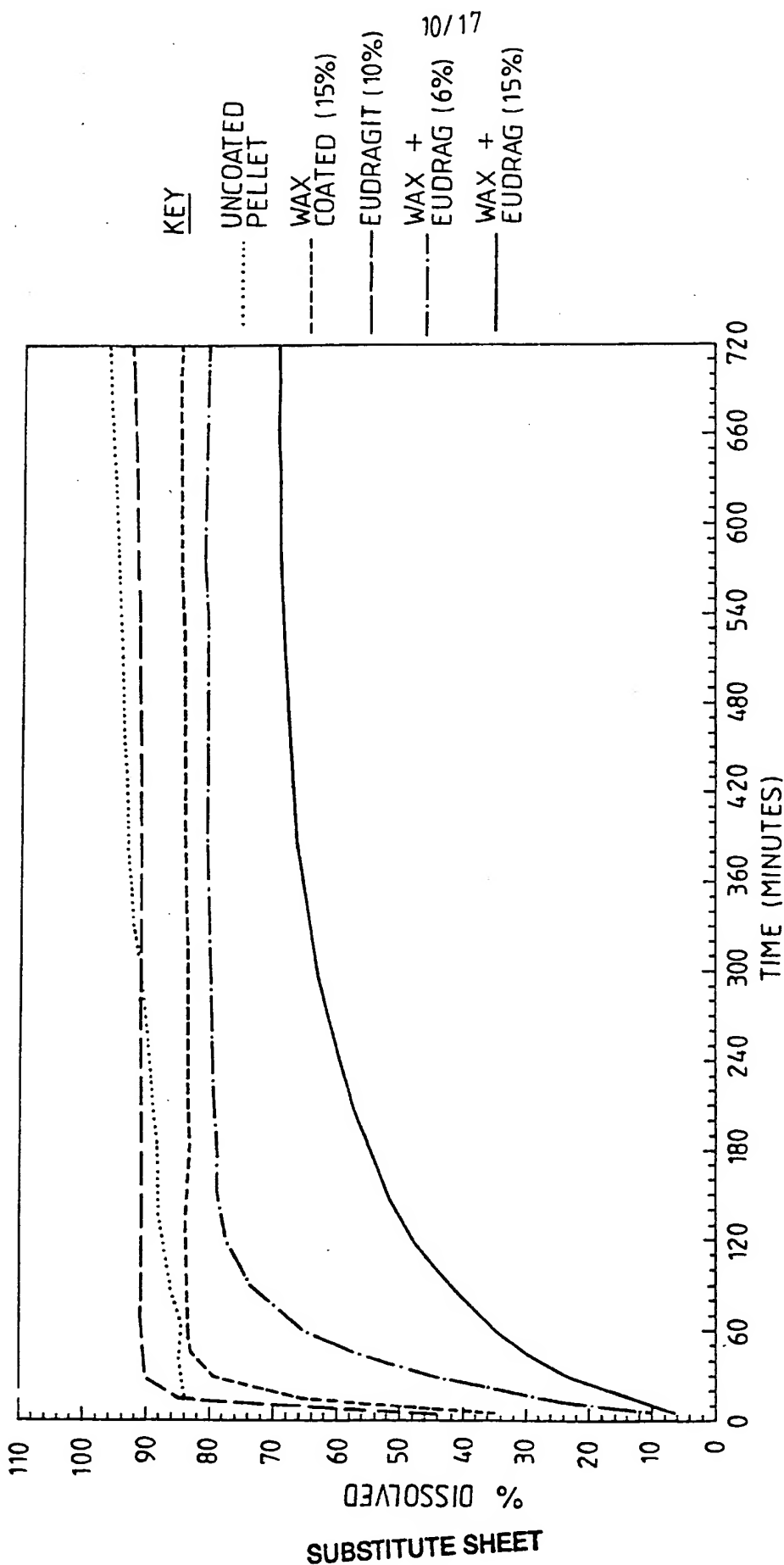
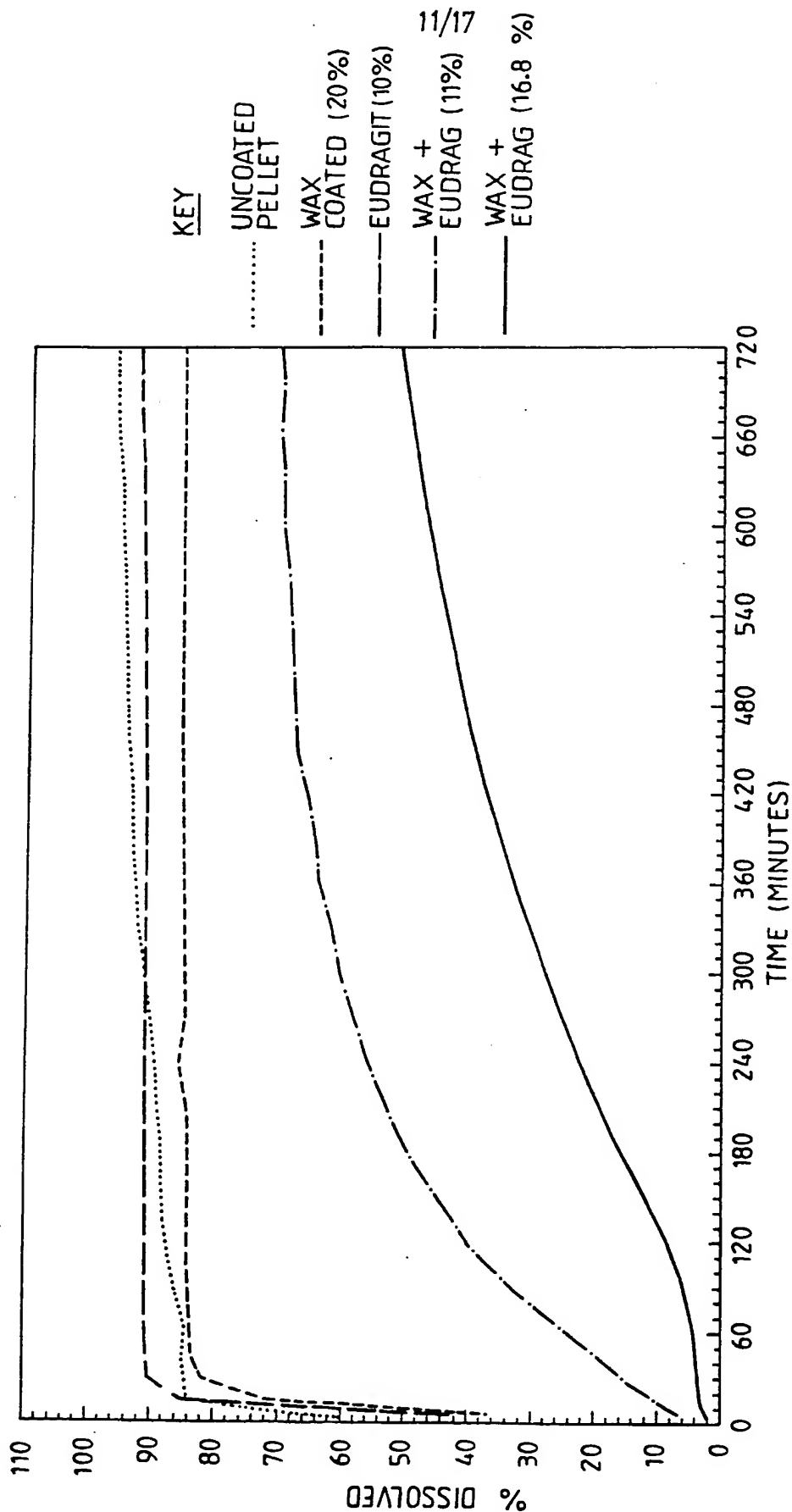
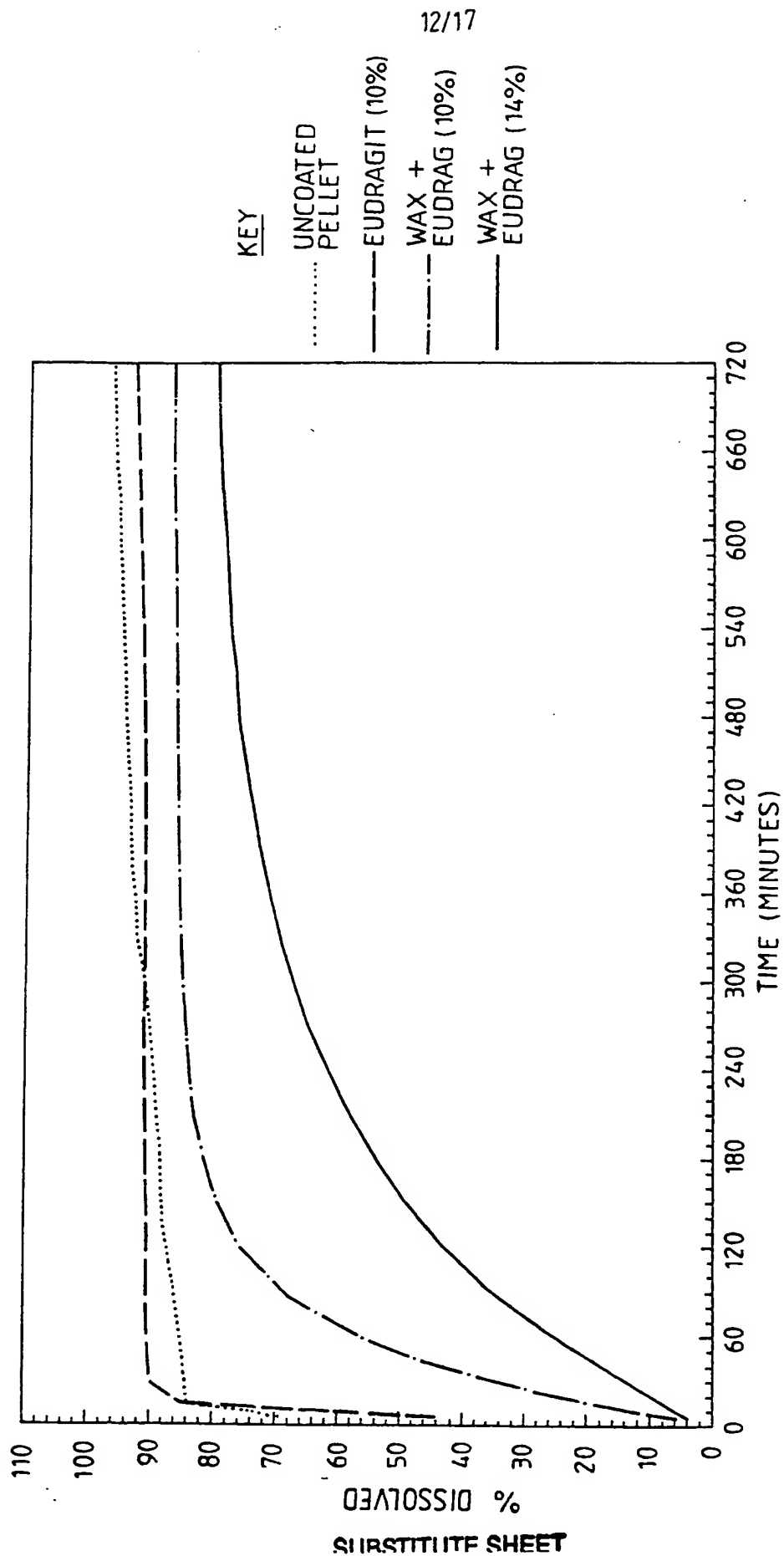


Fig.10 OXPRENOLOL HYDROCHLORIDE DISSOLUTION RESULTS  
WAX: TRISTEARIN



**Fig. 11** OXPRENOLOL HYDROCHLORIDE DISSOLUTION RESULTS  
WAX: CETOSTEARYL ALCOHOL



**Fig. 12** OXPRENOLOL HYDROCHLORIDE DISSOLUTION RESULTS  
WAX: WITEPSOL E85

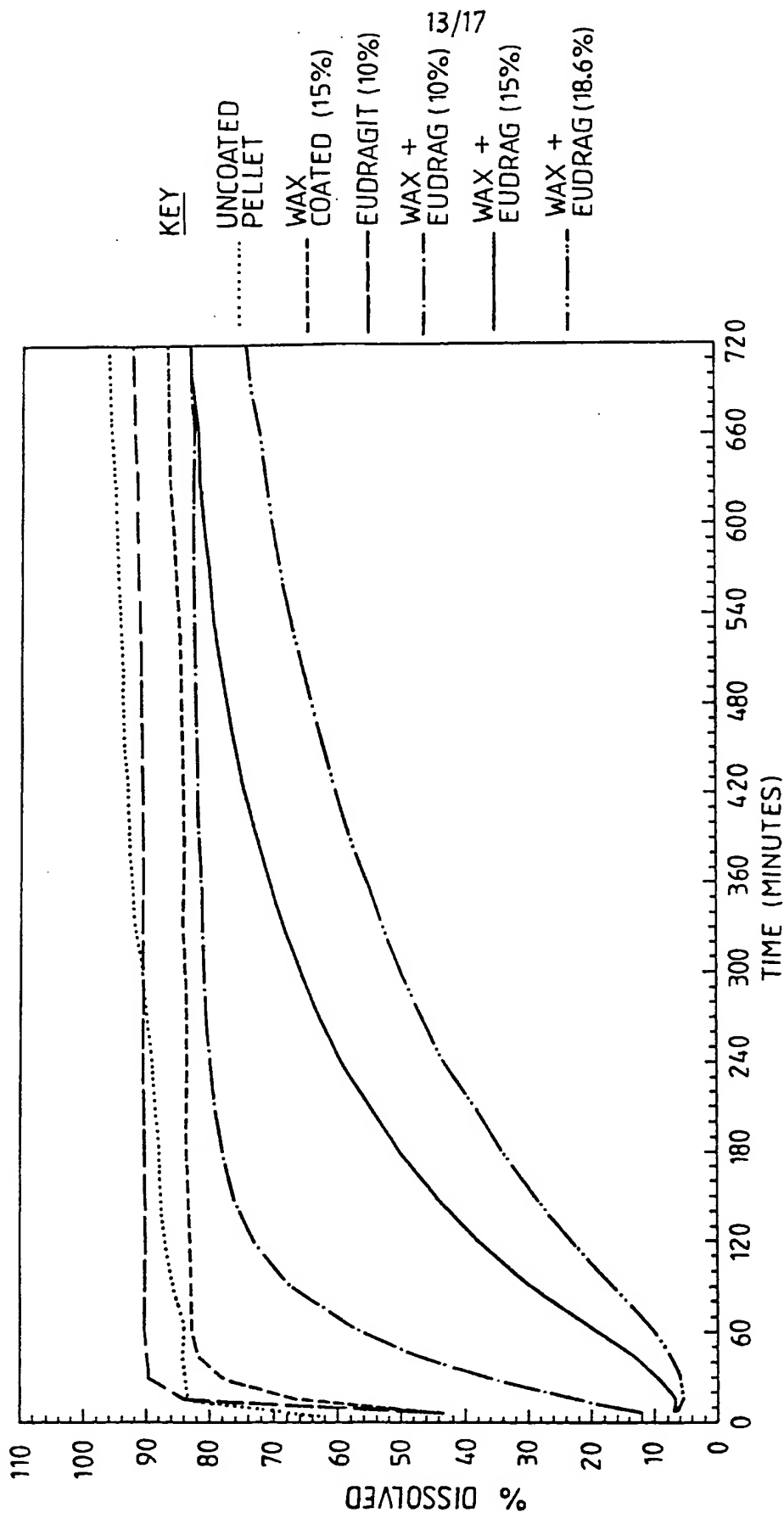


Fig.13 OXPRENOLOL HYDROCHLORIDE DISSOLUTION RESULTS  
WAX: DYNASAN 118

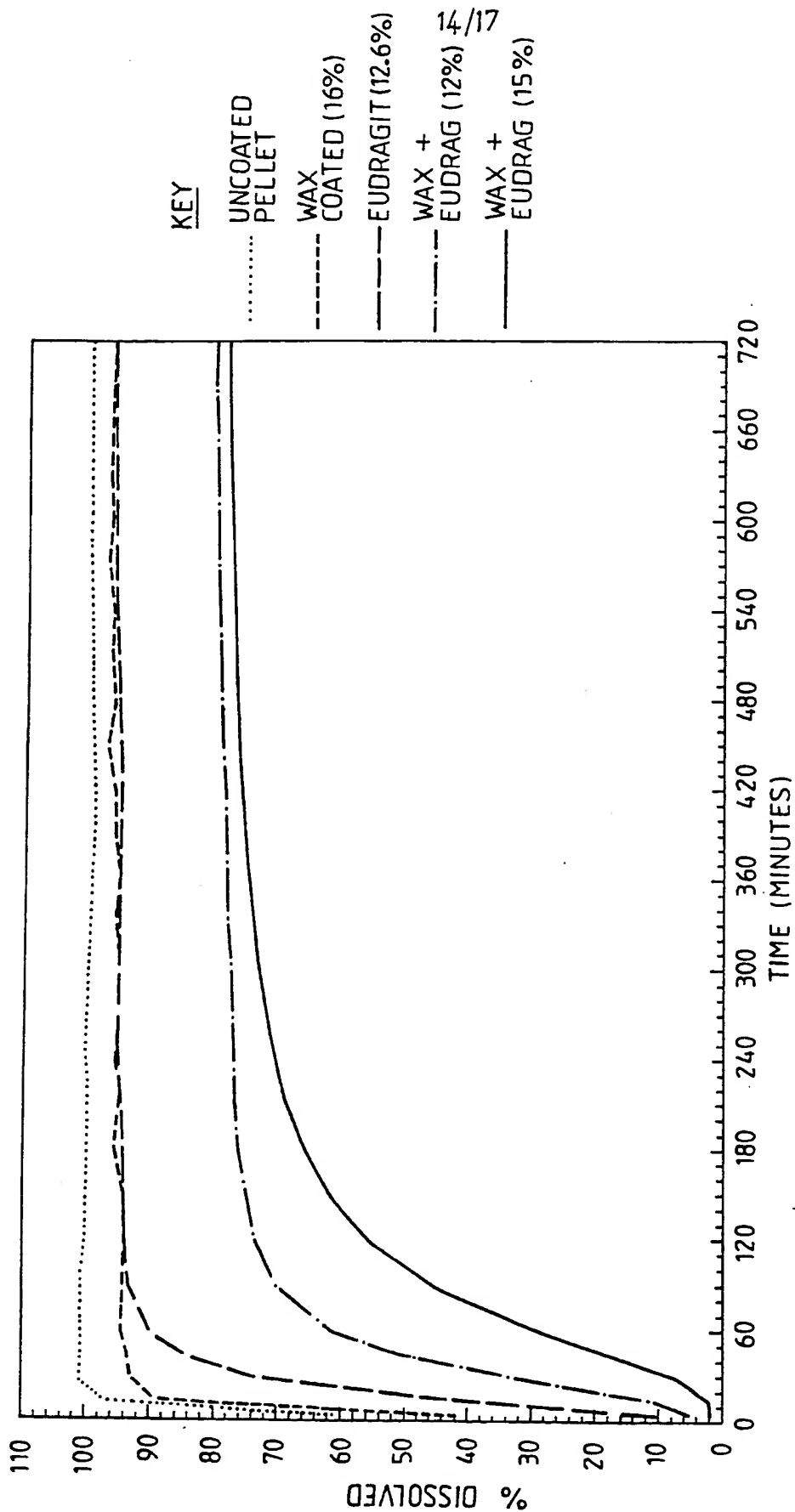


Fig.14 DIHYDROCODEINE TARTRATE DISSOLUTION RESULTS  
WAX: STEARYL ALCOHOL

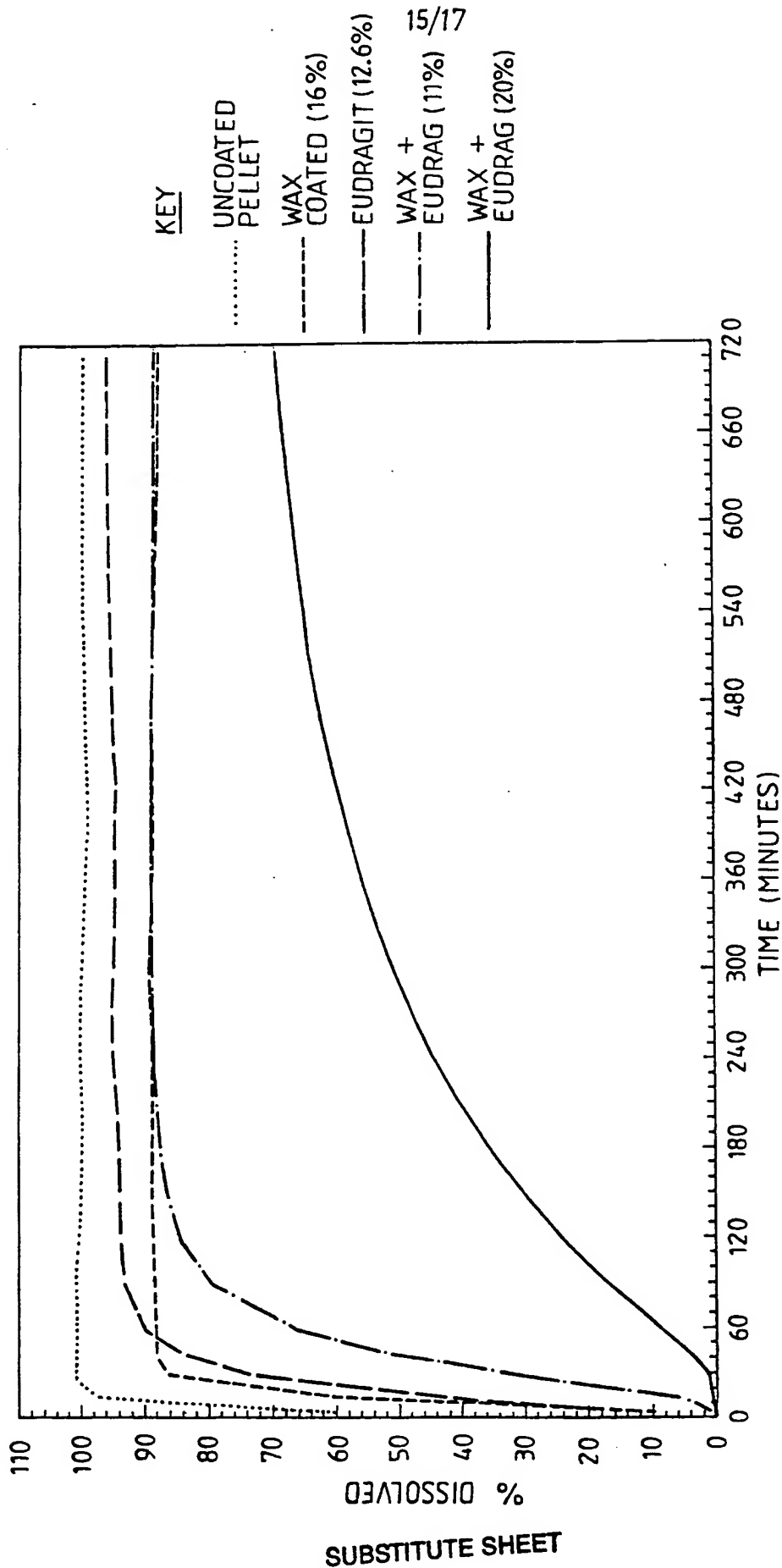


Fig. 15 DIHYDROCODEINE TARTRATE DISSOLUTION RESULTS  
WAX: CETOSTEARYL ALCOHOL

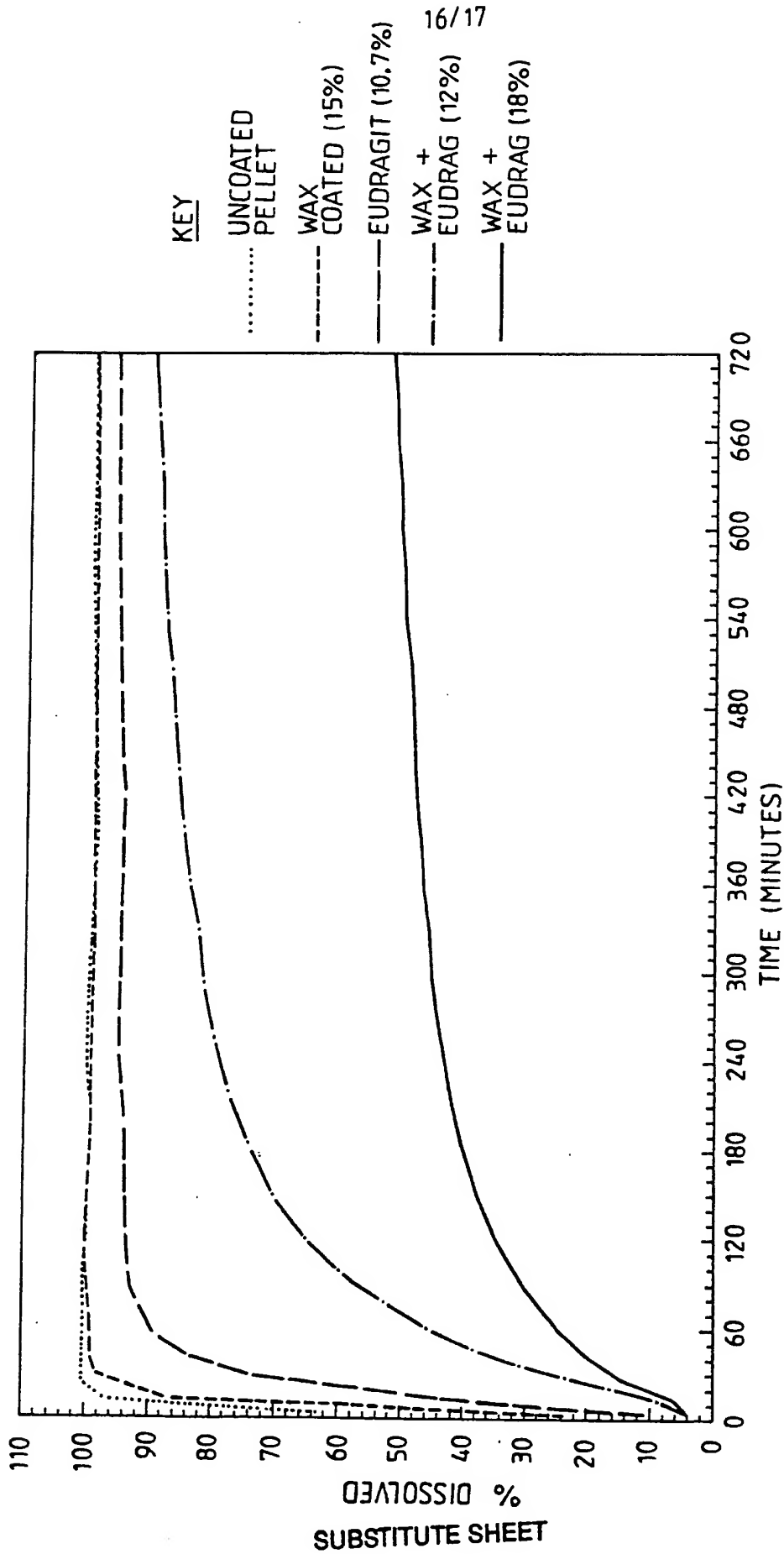


Fig.16 DIHYDROCODEINE TARTRATE DISSOLUTION RESULTS  
WAX: WITEPSOL E85

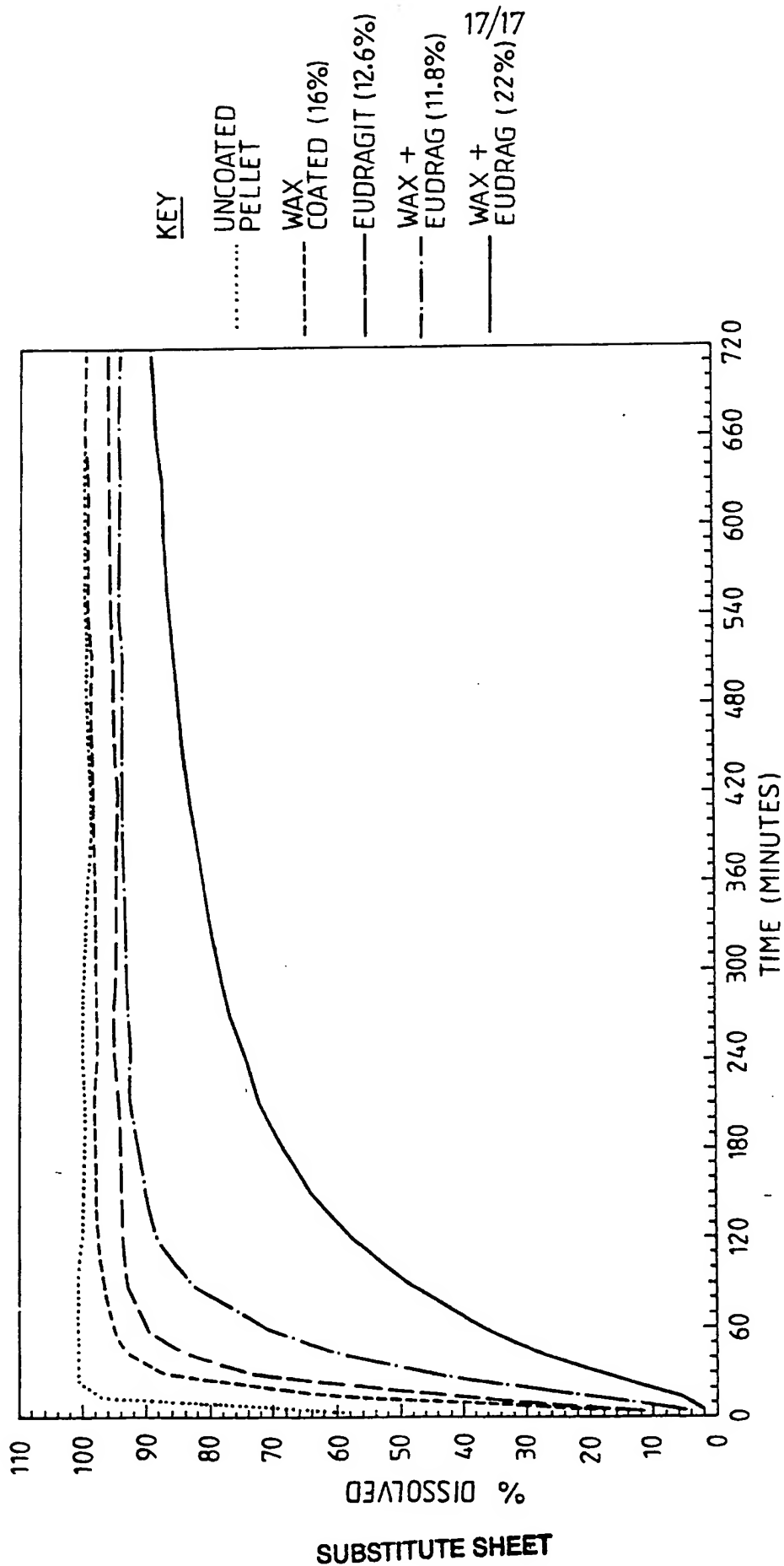



Fig. 17 DIHYDROCODEINE TARTRATE DISSOLUTION RESULTS  
WAX: DYNASAN 118

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 91/01153

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5                      A 61 K    9/50                      A 61 K    9/54		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.C1.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	EP,A,0263083 (R. VALDUCCI) 6 April 1988, see the abstract; page 2, column 2, lines 4-34; examples 4,5; claims ---	1-3,11, 13-15
X	Derwent File Supplier WPIL, 1990, AN 90-004022[01], Derwent Publications Ltd, (London, GB), & JP, A, 1287019 (TANABE SEIYAKU K.K.) 17 November 1989, see the abstract ---	1-3
Y	---	5-12,15 ,16
Y	WO,A,8902738 (APS RESEARCH LTD) 6 April 1989, see the abstract; example; claims ---	5-12,15 ,16
X	EP,A,0253684 (SHIONOGI SEIYAKU) 20 January 1988, see the abstract; page 2, lines 43-49; page 3, lines 8-12; examples 8-13; claims --- -/-	1,2,13
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
20-09-1991		17. 10. 91
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		 M.M. van der Drift

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		Relevant to Claim No.
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	
Y	---	5-12, 15, 16
Y	EP, A, 0255404 (APS RESEARCH LTD) 3 February 1988, see the abstract; claims	5-12, 15, 16
X	--- Chemical Abstracts, vol. 95, no. 1, 6 July 1981, (Columbus, Ohio, US), M. Ahmed et al.: "Formulation and evaluation of sustained release paracetamol tablets", see page 359, abstract 12671u, & J. Clin. Hosp. Pharm. 1981, 6(1), 27-38	1-4, 12
X	--- US, A, 3078216 (MARTIN GREIF et al.) 19 February 1963, see column 2, lines 26-41; column 3, lines 26-43; examples 1-6; claims	1, 11, 12
X	--- GB, A, 1340921 (PHARMACIA AS) 19 December 1973, see example 1; claims 1-8, 15	1, 2, 11, 12
A	--- Derwent File Supplier WPIL, 1985, AN 85-293614[47], Derwent Publications Ltd, (London, GB), & JP, A, 60202801 (NIHON TOKUSHU) 14 October 1985, see the abstract	1-3, 5-6
X	--- Derwent File Supplier WPIL, 1987, AN 87-096349[14], Derwent Publications Ltd, (London, GB), & JP, A, 62010012 (FUJISAWA PHARM.) 19 January 1987, see the abstract	1-3, 5, 12
X	--- WO, A, 8704070 (RESEARCH CORP.) 16 July 1987, see the abstract; page 5, line 9 - page 6, line 11; claims	1-3
A	--- EP, A, 0234078 (OHKAWARA KAKOHI CO.) 2 September 1987, see the abstract; column 5, line 1 - column 6, line 3	1-16
A	--- US, A, 3432593 (M. SHEPARD et al.) 11 March 1969, see example 2; claims 4, 7-9, 10-12	1-4, 11-15

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9101153  
SA 49457

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 07/10/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0263083	06-04-88	AU-B- 602931	01-11-90
		AU-A- 8025987	21-04-88
		WO-A- 8802253	07-04-88
		JP-T- 1500998	06-04-89
WO-A- 8902738	06-04-89	EP-A- 0386023	12-09-90
		JP-T- 3500288	24-01-91
EP-A- 0253684	20-01-88	JP-A- 63027424	05-02-88
		US-A- 4828840	09-05-89
EP-A- 0255404	03-02-88	JP-A- 63107917	12-05-88
		US-A- 4900558	13-02-90
US-A- 3078216		None	
GB-A- 1340921	19-12-73	CA-A- 944692	02-04-74
		DE-A- 2128527	16-12-71
		SE-B- 376720	09-06-75
WO-A- 8704070	16-07-87	EP-A- 0321457	28-06-89
		US-A- 5023108	11-06-91
EP-A- 0234078	02-09-87	JP-A- 61174940	06-08-86
		US-A- 4675236	23-06-87
US-A- 3432593	11-03-69	DE-A- 1467976	16-01-69
		FR-A- 1471882	
		GB-A- 1125612	
		GB-A- 1125882	
		US-A- 3446767	27-05-69